REMARKS

The Advisory Action dated August 19 has been carefully considered. Applicants note that the Amendment submitted on August 4, 2010 was denied entry. Applicants therefore re-submit the amendment under 1.114, accompanied by remarks responsive to the Examiner's stated concerns re patentability over the applied references. As previously noted, claim 2 is amended to correct an improperly configured Markush claim and claim 1 is amended to further clarify that the detectable protecting groups of steps (a), (b) and (c) are the same. Applicants believe entry is warranted and respectfully request the same. There are no other substantive changes to the claims.

Claims 1-3, 13, and 15-22 remain pending and subject to current examination.

Rejection under 35 USC §103

The rejection of **claims 1-3, 12, 13, and 15-22** under 35 USC §103(a) as being unpatentable over US Patent No. 6,238,862 to McGall et al (McGall), and Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997 (Wagner), in view of US Patent No. 5,151,507 to Hobbs et al (Hobbs) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and Agris (PGPUB 20020045167; 4/18/2002; cited previously) is maintained for reasons of record.

In response to Applicants' argument that McGall is deficient as a primary reference because the test methods of McGall destroy the chip for purposes of its intended downstream function, the Examiner responded that (1) she "can find no teaching or suggestion anywhere in McGall that the tested arrays are consumed or otherwise destroyed." The Examiner also contends that (2) "it is unclear how the arrays could be consumed or destroyed in McGall, but not in the present invention if McGall is using the same detecting groups." Finally, the Examiner asserts that (3) Applicants' arguments are directed to what the user does with the chip after testing rather than what the testing procedure does to the array. For the reasons set forth below, Applicants emphatically disagree with these statements.

With respect to Examiner contention (1), Applicants submit that the Examiner fundamentally misconstrues the teachings of McGall, or else has failed to grasp the instant invention, or both. McGall is directed to methods which assess quality either by sampling selecting chips from a batch production of chips and subjecting the selected chips to qualitative analysis, or by designing specific test chips that undergo similar conditions as the production batch, such as handling, packaging and storage, wherein the test chips subjected to the conditions are thereafter removed and tested for the affect of the conditions on various quality parameters of the chip. With respect to deprotection, McGall teaches an embodiment

directed to assessing "deprotection efficiency," which tests the extent to which a test condition causes deprotection of synthesized oligos (see IV, column 8, beginning with line 53). The method is discloses as being useful for "optimizing deprotection methods during synthesis," however the quality control methods themselves are not disclosed as occurring during synthesis; rather, they are disclosed as acting upon fully synthesized test arrays. Notably, McGall teaches that the sequence –specific oligo-arrays are already produced (see step 1, line 61-62 and Figure) with the free terminal end of each oligo capped (protected). A test condition is imposed, the chip is washed exposing unprotected sites, and the chip is assessed for the extent of deprotection achieved by that test condition (bridging to column 9). In a more specific embodiment the unprotected oligos are measured by exposing them to a detectable label, such as a fluorescing label, which couples only to the deprotected site.

This is very different from the instant methods, which provide quality assessment of all chips constituting the production batch, because the quality control method is built into the synthesis of the chip itself. The McGall methods are not intended to be practiced on a chip that is placed back into production after testing, hence the methods are generally disclosed as comprising removal of the oligos for inspection, (see, e.g. column 2, lines 32-38; see also column 4, lines 29-39), or other harsh manipulations of the array. In the only working examples of McGall, Example A describes a chip specially designed to test efficiency of photo-deprotection. This is clearly not a production chip. The chip comprises six horizontal stripes of various protected monomers, with UV light intensity applied as a vertical function across the stripes. The read-out is set forth as Figure 13. Example B describes a test protocol where test chips are synthesized, and the trips are exposed to acids, alkali treatments and then fluorescent imaging to determine the extent of depurination upon exposure to acidic conditions.

Applicants urge the examiner simply to look at the independent claims of McGall, which define the basic McGall invention. Claim 1 is clear on its face..."a quality control process for manufacturing nucleic acid probe arrays by spatially directed nucleic acid synthesis in high volume and *testing arrays selected from among the high volume* manufactured. Claim 23 is the independent claim specifically directed to the deprotection efficiency embodiment. According to this claim, a chip is divided into test condition areas, exposed to the test condition, and analyzed. There is absolutely no teaching or suggestion in McGall of quality control methods built into the chip synthesis, so that every production chip is subject to the method, and where quality as it relates to deprotection may be monitored during synthesis by means that do not require removal of the chip from production.

Hence, with respect to Examiner contention (2), Applicants note that the reason the McGall methods result in destruction of the chip for downstream purposes, while the instant methods preserve the chip for its intended functioning, despite teaching similar blocking groups, is due to the fundamental differences in the methods themselves. McGall does not want to preserve the chip as a production chip. McGall has designated test chips, or else samples the production chips for test chips. McGall may therefore remove the oligos and subject them to more vigorous testing. The instant methods, which are practiced on every production chip, seek to preserve the chips for functional use. Hence the analytical methods employed must be indirect and must not result in detachment or destruction of the oligos. The instant invention, as disclosed and recited provides a method that permits ON-CHIP quality control so that the quality of every chip with respect to extent of deprotection is assessed before downstream use.

With respect to Examiner contention (3), Applicants note that their arguments in fact pertain to both the intended functioning of the chip after testing, and the impact of the testing on the chip, as these two concepts are integral to one another. The intended functioning of Applicants chips after testing is to enter the market as functional chips, whereas the intended functioning of the McGall chips after testing is to be discarded, since McGall teaches dedicated test chips. The impact of Applicants' methods on the chip is to retain integrity and usability of the chip, whereas the impact of McGall's methods on the chip is to foreclose its use as a functioning genomic chip. The former merely reflects the latter.

Finally, and critically, the instant invention provides, for the first time, a quality control method for assessing deprotection of side chain amino groups of the nucleobases. As instantly disclosed, complete deprotection of these reactive groups is essential to optimal functioning of the chip (see, page 3, lines 1-6). McGall fails to teach or suggest quality control methods relating to deprotection of the side amino groups. The disclosure relied on by the Examiner as supporting a "suggestion" of such methods, is no more than general disclosure of how affy-chips, or oligo array chips, are synthesized. As part of a discussion of light-directed oligonucleotide synthesis in general, McGall details selective photodeprotection and coupling cycles to form desired oligo arrays. Upon production of the desired array, McGall notes that photolabile groups may then be removed and the oligos may be capped, and "side chain protective groups, if present, are also removed."

Applicants emphatically deny that this sentence suggests quality control methods to assure complete deprotection of these groups. In fact, it merely states that removing the groups is desirable for the finished product...surely a well-known thesis in this art. There is no recognition of problems associated with incomplete deprotection, or suggestion that methods quality control methods should be

provided which assess and correct incomplete deprotection. There is no teaching or suggestion of labeling, detecting, or otherwise assessing deprotection of protected side groups.

Applicants do not dispute that the basic methods for on-chip synthesis were well known, or that protection and deprotection of active groups have been exploited to direct synthesis for more than a decade. Nor do Applicants dispute that protection of nucleobases is known. Indeed, Applicants point this out along with examples of commonly employed protecting groups in the Background section of the instant specification. Applicants further note that the secondary references Agris expressly discloses that extent of base deprotection upon deprotection after oligo synthesis is a known problem in the art (see, e.g. [0003]).

Applicants' invention addresses and solves the known problem, expressly recognized by Agris, of determining extent of deprotection of the nucleobase side chains (the active groups which do not participate in elongation of the oligo) of an oligo array after on-chip synthesis, while keeping the array intact and capable of functioning for its intended ultimate use. The instant inventive quality control methods hinge on the use of detectable nucleobase blocking groups which may be cleaved from the completed array without consumption or degradation of the array, and under conditions which do not otherwise destroy the integrity of the array.

Fundamentally, Applicants submit that McGall is deficient as a primary reference because there is no way to modify the methods of the McGall to achieve the instant inventive methods.

The Examiner applies Wagner for disclosure of methods of synthesis of various oligonucleotides using protected nucleotides and for teaching that a fluorescent label may be linked directly to the amino group of the nucleobases and for teaching detecting the protecting groups attached to the synthesized oligonucleotides and deprotection of the label attached nucleobase after the synthesis of the oligonucleotide, as well as for disclosure of certain elements recited in dependent embodiments. Applicants do not dispute that a nucleobase protecting group has been known since 1990 and that methods for manufacturing oligo arrays comprise the step of protecting and then deprotecting the side chain amino reactive groups. Although Wagner discloses the dnseoc group for protection of the amino groups on the nucleobases, and deprotection at the end of synthesis, there is no teaching or suggestion of methods which assess the quality of deprotection on the array. The only method disclosed or suggested by Wagner with respect to deprotection efficiency comprises cleavage of the oligo from the array and assessment by rpHPLC (see page 205, lines 7-10). Hence, Wagner fails to teach use of a detectable

nucleobases protecting group as part of a quality control method for ensuring complete deprotection of nucleobases after synthesis of oligo arrays.

The secondary reference Agris recognizes the problem solved by the instant invention and is applied for allegedly teaching the need for methods of monitoring the degree of deprotection of nucleobases upon completion of synthesis of oligonucleotides on arrays by detecting detectable protecting groups "on the array." The Examiner argues that Agris teaches the need for "on-chip detection" so that simple and reliable techniques for determining the purity of the desired oligonucleotides on an array can be achieved. The Examiner argues that Agris provides a motivation to combine McGall and Wagner by stating the need to determine the degree of deprotection of the nucleobase side chains and the desirability for a simple and reliable technique to control the quality of the synthesized microarray. However, Applicants submit that the modification of McGall by Wagner in view of this suggestion by Agris does not result in the instant methods and the combination therefore does not enable the instant methods.

Agris specifically relates to provision of antibodies which bind to oligos having an organic protecting group covalently bound thereto (see Abstract, e.g.). In this way, one may determine the quantity of protecting groups remaining after synthesis. Once again, Applicants note that this sort of qualitative analysis destroys the integrity of the final chip product. Agris does not thereafter teach how one would remove the bound antibodies, perform additional deprotection steps if needed, and go through additional cycles of immunoassay to achieve complete deprotection. Agris merely quantifies the known problem. Agris also provides feedback to a practitioner that deprotection is not sufficient, but Agris fails to teach methods which permit quality assessment and correction to desired deprotection levels on the chip, whereafter the chip remains capable of its intended downstream function. Hence, Agris does nothing to overcome the enabling deficiency of McGall and Wagner.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). The combination of McGall and Wagner, in view of Agris, fails to enable the instant invention. Without additional undue guidance, a person of ordinary skill in the art could not achieve a quality control method for deprotection of nucleobase protecting groups in accordance with the instant methods, which require deprotection of the amine-protected groups on the chip at the completion of array synthesis, where the chip is preserved for its intended function, as required by the instant methods. McGall teaches sampling and test-chip based quality control methods, and notes that amino-protecting groups are typically removed at the end of chip synthesis. Wagner teaches a detectable protecting group for amino-reactive functionalities. Agris teaches methods for determining the percentage of amino groups

left protected after synthesis of oligonucleotides, but does not teach such methods for oligo array synthesis and therefore does not overcome the deficiency with respect to lack of teaching or suggestion of on-chip methods incorporated into the synthesis of the chip. The combination fails to teach or suggest methods which may be performed on the chip, without compromising the integrity of the chip, and which ensure complete deprotection of the amino side chain functionalities.

Claim 1 and dependent claims 2-3, 13, and 15-22 are therefore nonobvious and patentable under 35 USC §103 over McGall and Wagner in view of Agris, further in view of Hobbs and Chen. Reconsideration is therefore respectfully requested.

Respectfully submitted,

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